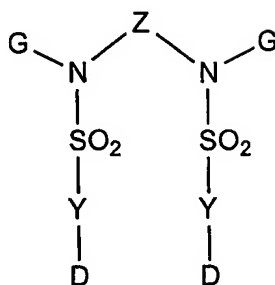


**CLAIMS:**

5

1. A compound having the formula (I):



(I)

including pharmaceutically acceptable salts, metal chelates, hydrates and solvates of the compound of formula (I); wherein

10 Y groups may be the same or different at each occurrence, each being selected from a bicyclic aromatic or heteroaromatic system of 8, 9 or 10 atoms in the cyclic nucleus; said aromatic or heteroaromatic system optionally being substituted by at least one of a halogen or a  $-\text{NO}_2$  group and wherein said heteroaromatic system comprises at least one heteroatom selected among N, O and

15 S;

G groups may be the same or different and are selected independently among hydrogen,  $-(\text{CH}_2)_m\text{CH}(\text{NH}_2)(\text{COOH})$  and  $-(\text{CH}_2)_m(\text{COOH})$ ; m being an integer selected among 1,2,3 and 4;

D is  $\text{WR}_b$ , wherein W is selected among null, N, O and C;

20 R represents a hydrogen, linear or branched alkyl of 1, 2, 3 or 4 carbon atoms, or  $-(\text{CH}_2)_m\text{CH}(\text{NH}_2)(\text{COOH})$ , wherein m is an integer of 0, 1,2,3 or 4; R moieties may be either the same or different; and

in the case that W is an oxygen atom, b is 1

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in the case that W is a nitrogen atom, b is 1 or 2;

and in the case that W is a carbon atom, b is 3;

Z is a group having the formula -U(G)(M)-T-U(G)(M)-;

wherein G groups may have the same meanings as above at each occurrence;

5 M groups may be the same or different, and are each independently selected from null, hydrogen, alkyl-amide, hydroxyalkyl and fluoroalkyl, wherein said alkyl has 1, 2 or 3 carbon atoms;

U groups may be the same or different, and are each independently selected from null or an optionally substituted, linear or branched alkylene of 1, 2, 3 or 4  
10 carbon atoms;

T is selected from -O-, -S-, -NH-, -N(B)-, -Q-, and -N(B'-Q)-, -N(B'-OH)-, -and -N(B'-F)- wherein B is an optionally substituted alkyl of 1, 2, 3, 4, 5 or 6 carbon atoms and B' is an optionally substituted alkylene of 1, 2, 3, 4, 5 or 6 carbon atoms;

15 Q is selected from a marker for imaging and a metal chelate; said marker for imaging being selected from the group comprising a fluorescent label, a radio-label, a marker for X-ray, a marker for MRI, a marker for PET scan, or a label capable of undergoing an enzymatic reaction that produces a detectable color;

2. The compound of Claim 1, wherein Q is a metal chelate.

20 3. The compound of Claim 2 wherein the metal is selected among Technetium, oxo-Technetium, Gallium, Rhenium or oxo-Rhenium isotopes

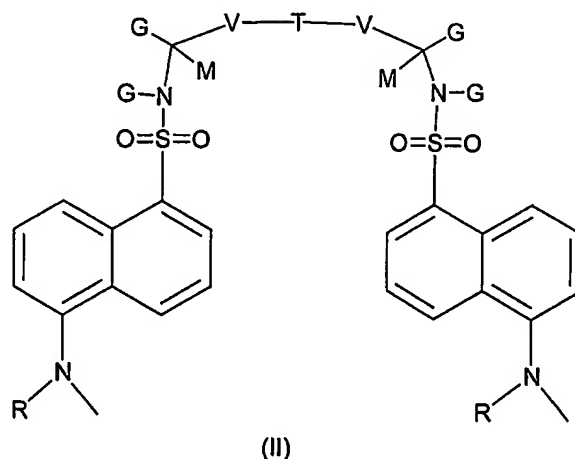
4. The compound of Claim 1, wherein Q is selected among  $^{18}\text{F}$  and  $^{124}\text{I}$ .

5. The compound of Claim 4, wherein Q is covalently linked to a Y or a D moiety, wherein Y and D are each as defined in Claim 1.

25 6. The compound of any one of Claims 1-5, wherein U at each occurrence is independently selected among null and an optionally substituted  $\text{C}_1\text{-C}_3$  alkylene group; D is  $\text{NR}_2$ , wherein each R group is selected independently from hydrogen and  $\text{C}_1\text{-C}_4$  alkyl.

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7. The compound of Claim 2, where the chelation of the metal of Q is accomplished through a combination of nitrogen, sulfur and/or oxygen atoms comprised in Q.
8. The compound of Claim 7, wherein the chelation of the metal of Q is accomplished through a combination of three nitrogen atoms and a sulfur atom, two nitrogen atoms and two sulfur atoms or a nitrogen atom and three sulfur atoms.
9. The compound of Claim 8, wherein the metal chelator of Q is selected from diaminedithiols, monoamine-monoamide-bisthiols (MAMA), triamide-monothiols, and monoamine- diamide-monothiols.
10. The compound of Claim 7, wherein the chelation of the metal of Q is accomplished through oxygen atoms.
11. The compound of Claim 1 having the following formula (II):



15

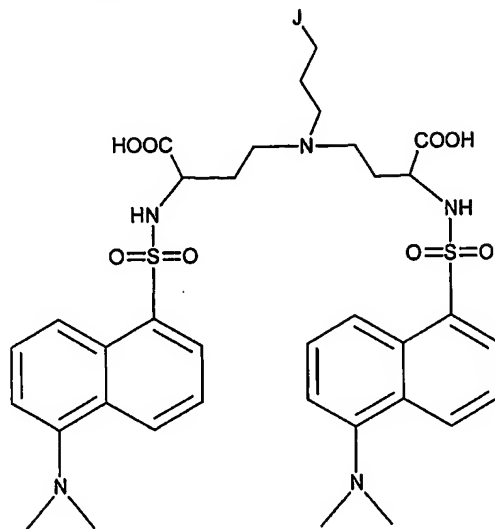
including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of the formula II;

wherein G groups may be the same or different and are selected independently among hydrogen,  $-(CH_2)_m(COOH)$  and  $COOH$  wherein m is an integer of 1, 2 or 3; V groups may be the same or different and are selected among null or  $-(CH_2)_k$ ; k being 1 or 2;

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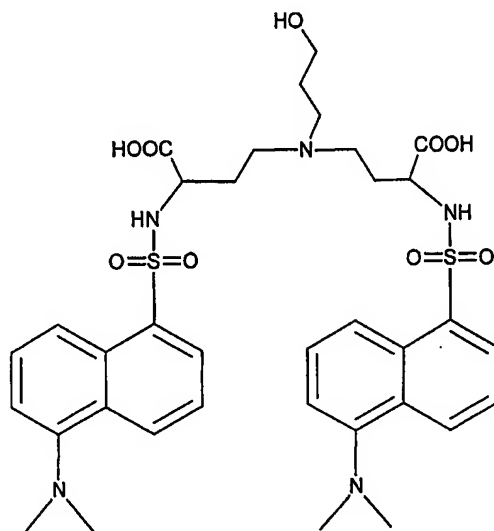
12. and T, M and R are as defined in Claim 1 The compounds of Claim 11 having the following formula (III):



(III)

wherein J is selected among hydrogen, -OH, and -Q; wherein said Q is selected  
 5 among an  $N_2S_2$  chelator and -F;  
 including pharmaceutically acceptable salts, hydrates, solvates and metal chelates  
 of the compound of the formula III.

13. The compound of Claim 12 having the following formula (IV):

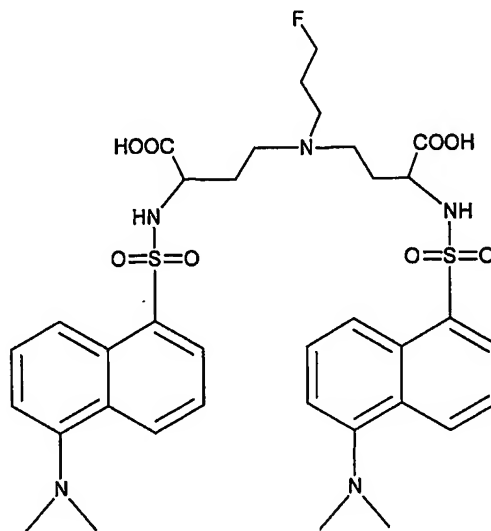


(IV)

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including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of the formula IV.

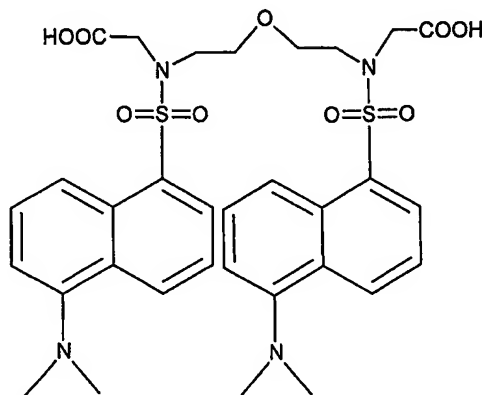
- 5 14. The compound of Claim 12 having the following formula V:



(V)

including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (V).

15. The compound of Claim 11 having the following formula VI:

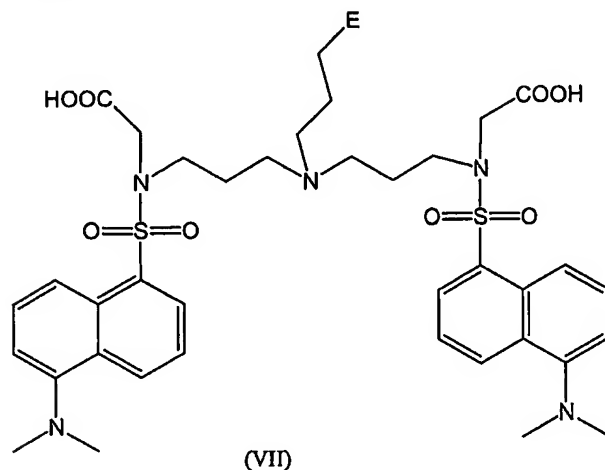


(VI)

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including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (VI).

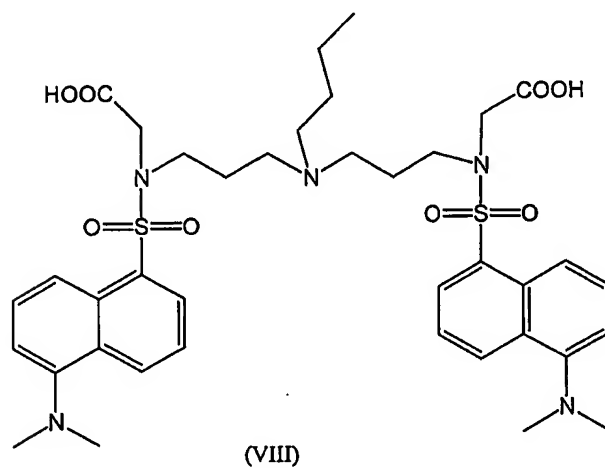
16. The compounds of Claim 11 having the following formula VII:



5        wherein E is selected from -OH, -F, -CH<sub>3</sub> and Q; wherein said Q is selected from an N<sub>2</sub>S<sub>2</sub> chelator and -F ;

including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (VII).

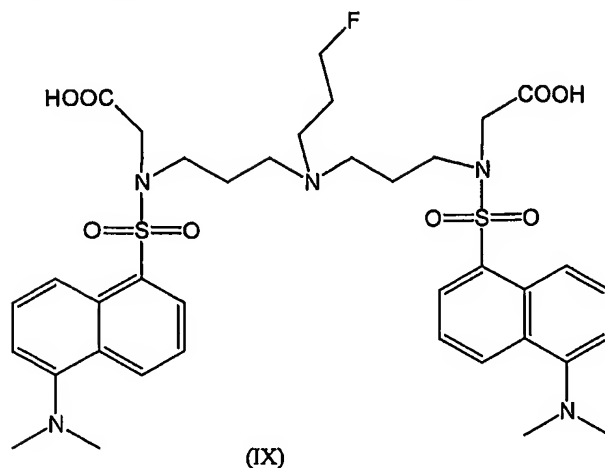
17. The compound of Claim 16 having the following formula VIII:



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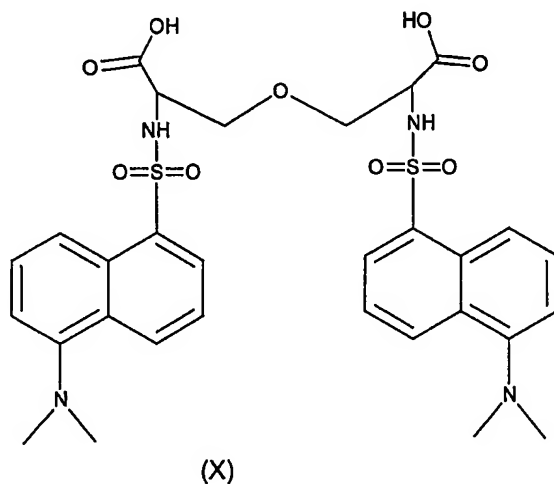
including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (VIII).

18. The compound of Claim 16 having the following formula IX:



including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (IX).

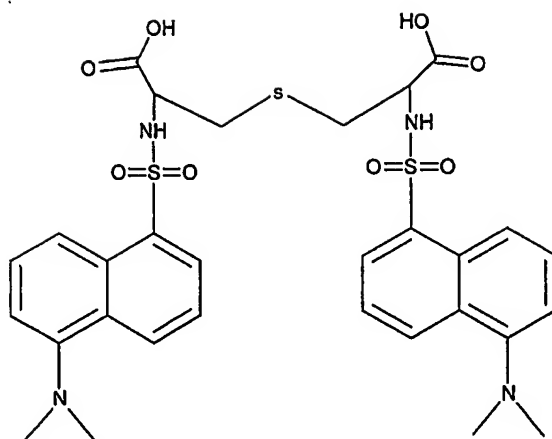
5 19. The compound of Claim 11 having the following formula X:



including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (X).

20. The compound of Claim 11 having the following formula XI:

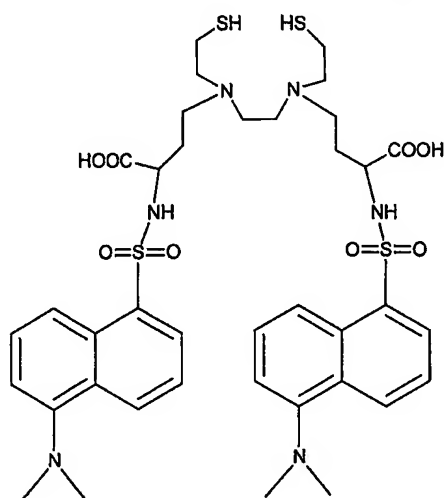
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(XI)

including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of formula (XI).

21. The compound of Claim 11 having the following formula XII:



(XII)

5

including pharmaceutically acceptable salts, hydrates, solvates and metal chelates of the compound of the formula XII.

22. The compound of any one of Claims 11, 12, 16 and 20 wherein the chelated metal is selected among Technetium, oxo-technetium, Rhenium and oxo-rhenium radioisotopes.

10

23. The compound of anyone of Claims 1 to 22 for use in the diagnosis of medical disorders in which cells undergo PNOM.



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24. A diagnostic agent comprising a compound of the formula I as defined in anyone of Claims 1 to 23 and a metal, said metal being comprised within the Q moiety of the compound of Claim 1.
25. A diagnostic agent being a compound of the formula I as defined in anyone  
5 of Claims 1 to 23, wherein Q is or comprises a radioisotope.
26. A diagnostic agent being a compound of the formula I as defined in anyone of Claims 1 to 23, having fluorescence properties.
27. A diagnostic kit comprising one or more vials containing a sterile formulation comprised of a predetermined amount of a diagnostic agent according  
10 to anyone of Claims 24-26 and optionally other components, such as stabilization aids, solubilization aids or bacteriostats.
28. A diagnostic kit according to Claim 27, wherein the one or more vials that contain all or part of the formulation can independently be in the form of a sterile solution or a lyophilized solid.
- 15 29. A diagnostic composition for the detection of a perturbed membrane in a sample of biological cells, *in vitro*, *ex vivo*, *in vivo* or for clinical imaging, comprising as an active component a compound of the formula I as defined in anyone of Claims 1 to 23, together with a biologically acceptable carrier, said active component having detectable properties of its own, being capable of chelating a  
20 detectable label or being covalently-linked to a detectable label.
30. The diagnostic composition of Claim 29, wherein said detectable label is a metal.
31. The diagnostic composition of Claim 29, wherein the active compound has detectable properties in its own, being detected by a fluorescent microscope, or by a  
25 flow-cytometric equipment.
32. The diagnostic composition of Claim 29, wherein the active compound has detectable properties in its own, for detection by radio-imaging techniques.
33. The diagnostic composition of Claim 30, being a diagnostic radio-composition for radio-imaging, wherein the active compound is in the form  
30 of a metal chelate, and said metal is a radioisotope.

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34. The diagnostic composition of Claim 33, for use in single photon emission computed tomography (SPECT), wherein the metal is a radioisotope of a metal selected from Tc, In, Cu, Ga, Xe, Tl and Re.
35. The diagnostic composition of Claim 34 wherein the metal is a radioisotope  
5 of a metal selected from Tc and Re.
36. The diagnostic radio-composition of Claim 35, wherein the active compound is radiolabeled with  $^{99m}\text{Tc}$ .
37. The diagnostic composition of Claim 29, being a diagnostic radio-composition for radio-imaging, wherein the radiolabel is a covalently linked  
10 radioisotope.
38. The diagnostic composition of Claim 37, being a diagnostic radio-composition for single photon emission computed tomography (SPECT).
39. The diagnostic composition of Claim 38, wherein the radiolabel is a radioisotope of iodine.
- 15 40. The diagnostic composition of Claim 29, being a diagnostic radio-composition for positron emission tomography (PET), wherein the radiolabel is a covalently linked radioisotope.
41. The diagnostic composition of Claim 40, wherein the radioisotope is selected from  $^{18}\text{F}$ ,  $^{15}\text{O}$ ,  $^{18}\text{O}$ ,  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{124}\text{I}$ ,  $^{13}\text{N}$  and  $^{75}\text{Br}$ .
- 20 42. The diagnostic composition of Claim 41, wherein the radioisotope is  $^{18}\text{F}$ .
43. The diagnostic composition of Claim 29 being a MRI contrast composition.
44. The diagnostic composition of Claim 43, wherein the active compound is in the form of a metal chelate, the metal being a paramagnetic metal ion.
45. The diagnostic composition of Claim 44 wherein said paramagnetic metal  
25 ion is selected from Gd(III), Fe(III) and Mn(II)
46. The diagnostic composition of Claim 29 being an X-ray or computerized tomography (CT) contrast composition.
47. The diagnostic composition of Claim 46 wherein the contrast composition comprises a contrast agent selected from Ba, Cs, Re, Rh, Ag, Ir or iodine.

48. The agent of anyone of Claims 24-26 for use in the diagnosis of medical disorders in which cells undergo PNOM.

49. The agent of anyone of Claims 24-26 for the detection of cells undergoing a death process.

5 50. The agent of Claim 49 for the detection of cells undergoing apoptosis.

51. The agent of anyone of Claims 24-26 for the detection of procoagulant particles, selected among activated platelets, platelet-derived microparticles, and apoptotic bodies.

52. The agent of anyone of Claims 24- 26 for the detection of a blood clot.

10 53. The agent of Claims 24- 26 for the detection of activated inflammatory cells, selected among activated white blood cells and activated tissue macrophages.

54. The agent of Claim 48, for detecting the presence of a disease condition in a person already known to have the disease, for the purposes of evaluating the disease severity, monitoring disease progression, and/or monitoring a response to  
15 therapeutic modalities.

55. The agent of Claim 48, for the detection and diagnosis of a disease selected from:

diseases characterized by occurrence of excessive apoptosis, degenerative disorders, neurodegenerative disorders, Parkinson's disease, Alzheimer's disease,  
20 Huntington chorea, AIDS, myelodysplastic syndromes, ischemic or toxic insults, graft cell loss during transplant rejection;

diseases manifested by excessive blood clotting; arterial or venous thrombosis, thrombo-embolism, myocardial infarction, cerebral stroke, deep vein thrombosis, disseminated intravascular coagulation (DIC), thrombotic  
25 thrombocytopenic purpura (TTP), sickle cell diseases, thalassemia, antiphospholipid antibody syndrome, systemic lupus erythematosus;

inflammatory disorders, and / or diseases associated with immune-mediated etiology or pathogenesis; auto-immune disorders, antiphospholipid antibody syndrome, systemic lupus erythematosus, connective tissue disorders such as  
30 rheumatoid arthritis, scleroderma; thyroiditis; dermatological disorders, pemphigus,

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erythema nodosum; autoimmune hematological disorders; autoimmune neurological disorders, myasthenia gravis; multiple sclerosis; inflammatory bowel disorders, ulcerative colitis; vasculitis.

56. The agent of Claim 54, wherein said detection is used to monitor adverse  
5 effects of anti-cancer treatments.

57. The agent of Claim 54, wherein said detection is used to monitor death of tumor cells is response to anti-cancer treatment, selected among chemotherapy and radiotherapy.

58. The agent of Claim 54, wherein said detection is used to characterize the  
10 intrinsic apoptotic load within a tumor, the level of aggressiveness of a tumor, or to detect metastases.

59. The agent of Claim 54, wherein said detection is used to monitor graft survival after organ transplantation.

60. The agent of Claim 54, wherein said detection is used for diagnosis of  
15 atherosclerotic plaques.

61. The agent of Claim 54, wherein said detection is used in the monitoring of response to cytoprotective therapy in a disease characterized by excessive apoptosis, said response being inhibition of cell death.

62. A diagnostic kit comprising one or more vials containing a sterile  
20 formulation comprised of a predetermined amount of a diagnostic composition according to Claim 29 and optionally other components, such as stabilization aids, solubilization aids or bacteriostats.

63. A diagnostic kit according to Claim 62, wherein the one or more vials that contain all or part of the formulation can independently be in the form of a sterile  
25 solution or a lyophilized solid.

64. A method for the detection of cells having perturbed membranes (PM cells) in a cell sample, the method comprising:

(i) contacting the cell sample with a diagnostic agent according to anyone of Claims 24-26 under conditions enabling binding of said agent to biological  
30 membranes; and

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(ii) detecting bound agent to said cells; the presence of a significant amount of bound agent indicating the presence of PM in said cells.

65. A method for the detection of physiological disorders characterized by the presence of cells having perturbed membranes (PM cells), and/or medical disorders  
5 in which PM cells have an etiological or a pathogenetic role, such method comprising:

(1) administering a diagnostic composition according to any one of Claims 29-47 to a patient; and

(2) imaging the patient using an appropriate imaging technique.

10 66. A method according to Claim 65 wherein the diagnostic composition comprises a radiolabel, and the detection of the medical disorders is by a radio-imaging technique.

67. A method according to Claim 65 wherein the diagnostic composition comprises a radiolabel, and the detection of the medical disorders is by single  
15 photon emission computed tomography (SPECT).

68. A method according to Claim 65 wherein the diagnostic composition comprises a radiolabel, and the detection of the medical disorders is by positron emission tomography (PET).

69. A method according to Claim 65 wherein the diagnostic composition is an  
20 X-ray contrast agent.

70. A method according to Claim 65 wherein the diagnostic composition comprises a magnetic resonance imaging (MRI) contrast agent.

71. A method according to Claim 65 or 64 wherein the diagnostic composition comprises a fluorescent label.

25 72. A method according to Claim 65 or 64, for the detection of cells undergoing a death process.

73. A method according to Claim 72, for the detection of cells undergoing apoptosis.

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74. A method according to Claims 65 or 64, for the detection of procoagulant particles, selected among activated platelets, platelet-derived microparticles, and apoptotic bodies.
75. A method according to Claim 65 or 64 for the detection of a blood clot.
- 5 76. A method according to Claim 65 or 64, for the detection of activated inflammatory cells, selected among activated white blood cells and activated tissue macrophages.
77. A method according to Claim 65, for the diagnosis of a disease selected from:
- 10 diseases characterized by occurrence of excessive apoptosis; degenerative disorders, neurodegenerative disorders, Parkinson's disease, Alzheimer's disease, Huntington chorea, AIDS, myelodysplastic syndromes, ischemic or toxic insults, graft cell loss during transplant rejection;
- diseases manifested by excessive blood clotting; arterial or venous
- 15 thrombosis, thrombo-embolism, myocardial infarction, cerebral stroke, deep vein thrombosis, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), sickle cell diseases, thalassemia, antiphospholipid antibody syndrome, systemic lupus erythematosus; inflammatory disorders, and / or diseases associated with immune-mediated etiology or
- 20 pathogenesis; auto-immune disorders, antiphospholipid antibody syndrome, systemic lupus erythematosus, connective tissue disorders such as rheumatoid arthritis, scleroderma; thyroiditis; dermatological disorders, pemphigus, erythema nodosum; autoimmune hematological disorders; autoimmune neurological disorders, myasthenia gravis; multiple sclerosis; inflammatory bowel disorders,
- 25 ulcerative colitis; vasculitis.
78. A method according to Claim 65, for the detection of atherosclerotic plaques.
79. A method according to Claim 65, for detection of cell death within a tumor, for monitoring of aggressiveness of a tumor, or for detection of metastases of a
- 30 tumor.

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80. A method according to Claim 65, for monitoring death of tumor cells in response to an anti-cancer treatment, selected from chemotherapy and radiotherapy.
81. A method according to Claim 65, for monitoring of adverse effects of an anti-cancer treatment, wherein said adverse effects being death of normal cells.
- 5 82. A method according to Claim 65, for monitoring of survival of a grafted organ after transplantation.
83. A method according to Claim 65, for monitoring of response to cytoprotective therapy in a disease characterized by excessive apoptosis, said response being inhibition of cell death.